

Please cancel claim 16.

B<sub>2</sub> 17. (Amended) The antibody of claim 15 which is a humanized or human antibody.

B<sub>3</sub> D<sub>1</sub> 29. (Amended) A composition comprising the antibody of claim 15, and a carrier.

### REMARKS

#### Status of the claims

Pending claims 1-57 were subjected to a restriction requirement and species election. Applicants elect to prosecute Group II claims 15-21 and 29-33. Claims 1-14, 22-28 and 34-57 have been withdrawn as being directed to a non-elected invention due to the restriction. Claims 15 and 17 have been amended. Claim 15 is amended to incorporate claim 16. Claim 16 is now cancelled. Claim 17 is amended to change the dependency in view of the cancellation of claim 16 from which it previously depended. In view of the election of the Group II claims, claim 29 is amended to delete the dependency from claim 2 since claim 2 is a non-elected invention. Applicants reserve the right to prosecute any deleted subject matter as a result of this restriction, in a future application.

Upon entry of this amendment, claims 15, 17-21 and 29-33 will be pending. For the Examiner's convenience, an appendix of the pending claims, as amended, is attached herewith.

#### Restriction and Species Election

The Examiner has required restriction of the claims to one of the following groups under 35 U.S.C. §121:

- I. Claims 1-14, 29-33 and 56 (claim 29, as it reads on claim 2), drawn to an anti-prostate stem cell antigen antibody, classified in class 530, subclass 387.7.
- II. Claims 15-21 and 29-33 (claim 29, as it reads on claim 15), drawn to an anti-PSCA monoclonal antibody that inhibits the growth of PSCA expressing cells, classified in class 530, subclass 388.1.
- III. Claims 22-27, drawn to an isolated nucleic acid, vector, and host cell, classified in class 536, subclass 23.1.
- IV. Claim 28, drawn to a method of producing the antibody of claim 2, classified in class 435, subclass 70.1.
- V. Claims 34-45, drawn to a method of killing a PSCA-expressing cancer cell, classified in class 424, subclass 130.1.

VI. Claims 46-55 and 57, drawn to a method of alleviating PSCA-expressing cancer in a mammal, classified in class 424, subclass 141.1.

In response to the restriction requirement, Applicants hereby confirm the election of Group II (claims 15-21 and 29-33) (claim 29, as it reads on claim 15), drawn to an anti-PSCA monoclonal antibody that inhibits the growth of PSCA expressing cells, for prosecution.

However, Applicants traverse the requirement for a species election in each of Groups I and III claims.

With regard to the Group I claims, the Office is requiring election of a single species of antibody sequence from the species of SEQ ID NO. 10, 11, 12 and 13. With regard to the Group III claims, the Office is requiring election of a single species of antibody sequence from the species of SEQ ID NO. 3-13. The Office states that the species are patentably distinct based on structural and functional difference, modes of action and that the species may target different receptors.

Applicants submit that the antibodies bearing these sequences in the Markush group all specifically bind the same antigen, PSCA. It is not clear to Applicants what is implied by the remark that the species may target "different receptors".

#### Rejections under 35 U.S.C §102(e)

Claims 15-21 and 29-33 have been rejected under 35 U.S.C. §102(e) as allegedly anticipated by Reiter, et al., WO 98/40403. According to the Office, Reiter et al. disclose monoclonal antibodies that bind to PSCA which destroy prostate cancer cells. The Office further remarks that "It is inherent that the cytotoxic agent is a maytansinoid, the antibody is human, since it is derived from and used to treat human prostate cancer, and that the antibody is internalized upon binding to PSCA because PSCA is found both internally and externally."

Applicants traverse this rejection on the following grounds.

Independent claim 15 recites an anti-PSCA monoclonal antibody that inhibits the growth of PSCA-expressing cancer cells *in vivo*, wherein the antibody internalizes upon binding to PSCA on the cancer cell. Applicants have demonstrated that the anti-PSCA antibodies of the invention exhibit cytotoxic activity and do indeed inhibit the growth of PSCA-expressing cancer cells *in vivo* (see Examples 5, 7, 9 on pages 62-68). As elaborated below, Applicants have also demonstrated that the claimed antibodies internalize upon binding PSCA so that for certain embodiments of therapeutic use, the antibodies conjugated to a cytotoxic agent having an intracellular target can effectively deliver the cytotoxic agent into the cancer cell *in vivo*.

Anticipation requires that the prior art reference disclose every element of the claim. In addition, the reference must be enabling. *In re Donohue*, 226 USPQ 619, 621 (Fed. Cir. 1985). Reiter et al. on page 3, last paragraph, describes that "the invention provides antibodies capable of binding to PSCA which can be used therapeutically to destroy cancer cells." However, Reiter et al. provide no showing that their PSCA binding antibodies can inhibit the growth of PSCA-expressing cancer cells *in vivo* as is required by the present claims, or even *in vitro*. Nor does the Reiter reference show that their antibodies internalize upon binding to PSCA on the cancer cell.

The Office's remarks with regard to what is allegedly inherent are without clear basis and rather baffling. Applicants will address each of these allegedly inherent elements in order. Firstly, maytansinoids are a specific embodiment of toxins in the claims directed to compositions of immunoconjugates. There are many different cytotoxic agents with different mechanisms of action; the maytansinoid family is one class of such agents. Reiter et al. lists examples of cytotoxic agents on pages 13-14. However, nowhere in the Reiter reference is there a mention of maytansinoid toxins. How a maytansinoid is "inherent" in this context is unclear. Since the Reiter et al. reference fails to disclose the presently claimed compositions of anti-PSCA monoclonal antibody conjugated to maytansinoid, wherein the PSCA antibody has the properties of internalizing upon binding to PSCA on the cancer cell and inhibiting the growth of the cancer cells *in vivo*, the claimed invention was not contemplated and cannot be anticipated by this reference.

With regard to the remark that it is inherent that "...the antibody is human, since it is derived from and used to treat human prostate cancer", this rationale behind this statement is unclear. An antibody for human therapy does not imply that it is necessarily a human antibody. In fact, the therapeutic antibodies of date that are on the market for human therapy, for example, Remicade® (from Centocor), Herceptin® and Rituxan® (from Genentech), are murine, chimeric mouse-human or "humanized", the latter of which is different from "human" antibodies (see specification, e.g., at pages 8, 22-23 for definitions of human and humanized antibody).

With regard to the comment that "It is inherent ....that the antibody is internalized upon binding to PSCA because PSCA is found both internally and externally", Applicants believe there may be a misunderstanding of what "internalization" means. The specification on pages 10-11, and page 17, last paragraph, discuss "internalization" of a cell surface molecule and an antibody bound to the molecule. As described on page 2, paragraph one of the specification, PSCA is a GPI-linked molecule, which means it is tethered to the plasma membrane by a

glycosylphosphatidylinositol (GPI) linkage. Thus, PSCA is not present on the cell surface as a protein with a cytoplasmic inside or internal in the cell. Also, as discussed in the specification (page 17, last paragraph), it cannot be known *a priori* that an antibody to PSCA would be internalized upon binding to PSCA since internalization by GPI-linked molecules is not well studied and, as well, the ability of an antibody to internalize depends on various factors. Applicants have however, demonstrated that the anti-PSCA antibodies of the present invention are efficiently endocytosed and internalized both *in vivo* and *in vitro* (see Example 3, in particular, the last paragraph of page 61)

In view of the remarks above, Applicants submit that there can be no anticipation of the claimed invention by Reiter et al. and respectfully submit the withdrawal of this rejection under 35 U.S.C. §102(e). Applicants believe the pending claims are in condition for allowance.

If a telephone interview would be of assistance in advancing prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided below.

In the unlikely event that this transmittal letter is separated from this document and the U.S. Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Director to charge the cost of such petitions and/or other fees due in connection with the filing of this document to our Deposit Account No. 07-0630.

Respectfully submitted,

GENENTECH, INC.

Date: April 23, 2002

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**Version With Markings To Show Changes Made**

In the claims:



15. (Amended) An anti-PSCA monoclonal antibody that inhibits the growth of PSCA-expressing cancer cells in vivo, wherein the antibody internalizes upon binding to PSCA on the cancer cell.

17. (Amended) The antibody of claim 15 [16] which is a humanized or human antibody.

29. (Amended) A composition comprising the antibody of [claim 2 or] claim 15, and a carrier.

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APPENDIX OF PENDING CLAIMS AS AMENDED ON APRIL 23, 2002

15. (Amended) An anti-PSCA monoclonal antibody that inhibits the growth of PSCA-expressing cancer cells in vivo, wherein the antibody internalizes upon binding to PSCA on the cancer cell.
16. (Canceled) The antibody of claim 15, wherein the antibody internalizes upon binding to PSCA on the cancer cell.
17. (Amended) The antibody of claim 15 which is a humanized or human antibody.
18. The antibody of claim 17 which is produced in bacteria.
19. The antibody of claim 15, which is a humanized form of an anti-PSCA antibody produced by a hybridoma selected from the group of hybridomas having ATCC accession number PTA-717, PTA-718, PTA-719, PTA-720, PTA-880, or PTA-2265.
20. The antibody of claim 15, wherein the cancer cells are from a cancer selected from the group consisting of prostate cancer, bladder cancer and lung cancer.
21. The antibody of claim 20, wherein the cancer is prostate cancer.
29. (Amended) A composition comprising the antibody of claim 15, and a carrier.
30. The composition of claim 29, wherein the antibody is conjugated to a cytotoxic agent.
31. The composition of claim 30, wherein the cytotoxic agent is a maytansinoid.
32. The composition of claim 31, wherein the antibody is a human or humanized antibody and the carrier is a pharmaceutical carrier.
33. The composition of claim 32, wherein the humanized antibody is a humanized form of an anti-PSCA antibody produced by a hybridoma selected from the group of hybridomas having ATCC accession number PTA-717, PTA-718, PTA-719, PTA-720, PTA-880, or PTA-2265.